Inhibition of Angiotensin I-Initiated Hemodynamic Changes in Anesthetized Dogs by a Synthetic Nonapeptide (36413)

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A nonapeptide, Pyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro, isolated from the venom of *Bothrops jararaca*, potentiates bradykinin activity and inhibits the angiotensin-converting enzyme (1–3). SQ 20,881 is a synthetic nonapeptide, chemically and biologically identical to the natural peptide (3–5).

Parenteral administration of the pharmacologically inactive decapeptide, angiotensin I, which is converted in the circulation to the active octapeptide, angiotensin II, results in vasoconstriction, with an increase in blood pressure and a reduction in renal blood flow (6–8). SQ 20,881 competitively inhibits the angiotensin-converting enzyme and, thus, prevents the conversion of angiotensin I to angiotensin II (4, 5, 8).

The objectives of this study were to demonstrate the inhibitory effect of SQ 20,881 on angiotensin I-initiated changes in blood pressure and renal blood flow under the condition of an angiotensin I load, and to determine dose–response relationships for both degree and duration of inhibition.

Methods. Eight fasted male purebred beagles, 9 to 11 kg, were hydrated orally with water (50 ml/kg), anesthetized with intravenous pentobarbital sodium (30 mg/kg), intubated with an endotracheal tube, and maintained under light anesthesia by an intravenous infusion of pentobarbital sodium at the rate of 2.5 mg/kg during each hour.

Carotid arterial pressure and renal blood flow (electromagnetic flow probe on left renal artery) were recorded continuously for each animal. After stable base line control values for blood pressure and renal blood flow had been attained, an intravenous infusion of angiotensin I[1] (50 to 100 ng/kg/min) was started. After equilibration of the angiotensin I-initiated effects on blood pressure and renal blood flow, 45-sec intravenous injections of SQ 20,881 were given, according to the following schedule:

Dog	(μg/kg)
1	10, 30, and 30
2 and 3	10, 30, 100, and 300
4	100 and 300
5 and 6	300
7 and 8	1000

A succeeding dose of SQ 20,881 was given only if the arterial pressure and renal blood flow had returned to preinjection levels attained with the angiotensin I alone. The infusion of angiotensin I was interrupted periodically in order to confirm base line control values.

Results and discussion. Maximal inhibition and the duration of at least 25% inhibition by SQ 20,881 on the angiotensin I-initiated hemodynamic responses were determined for each dose. The data are presented in Figs. 1 to 4. In some instances, fluctuations in either base line or infusion control values for blood pressure or renal blood flow made it difficult to determine accurately the duration of inhibition caused by SQ 20,881. Consequently, there are fewer values in Figs. 3 and 4 than in Figs. 1 and 2.

The degree of inhibition of the pressor response was proportional to the dose of SQ 20,881, and reached a maximum (100%) at 1000 μg/kg (Fig. 1). The degree of inhibi-

[1] [Ile^5]-angiotensin I, Schwarz-Mann, Orangeburg, NY.

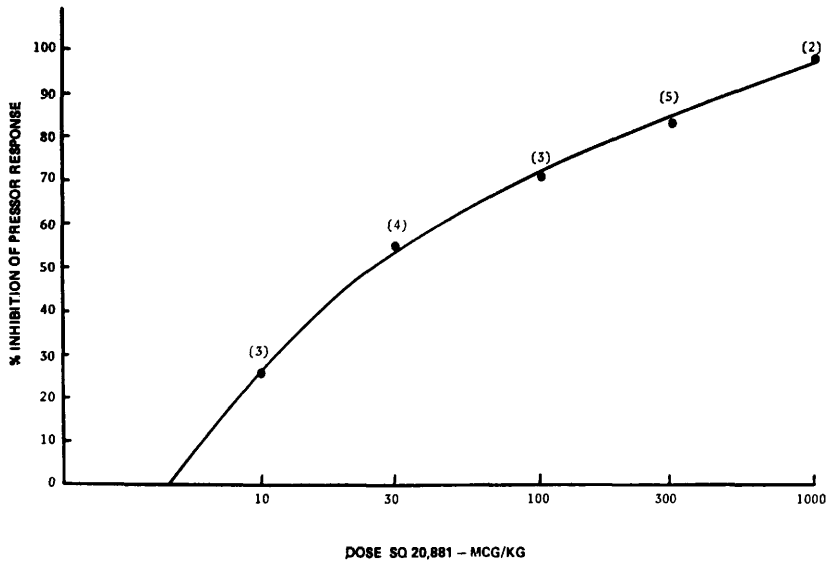

FIG. 1. Maximal inhibition of the angiotensin I-initiated pressor response by intravenous injections of SQ 20,881. Angiotensin I infused at 50 to 100 ng/kg/min. Points represent mean values of the number of doses in parentheses.

tion of the angiotensin I-initiated depression in renal blood flow was proportional to the dose of SQ 20,881 up to 300 μg/kg (Fig. 2); this dose produced a maximal inhibition of about 80%.

The duration of inhibition of both the pressor and reduced renal blood flow responses was proportional to the dose of SQ 20,881 up to 300 μg/kg (Figs. 3 and 4); this dose caused at least a 25% inhibition of the effects of angiotensin I for about 2 hr. In one dog, a 1000 μg/kg dose of SQ 20,881 inhibited the pressor response for more than 3 hr (Fig. 3).

Infusion control values for arterial pressure and renal blood flow were never significantly increased or decreased, respectively, after

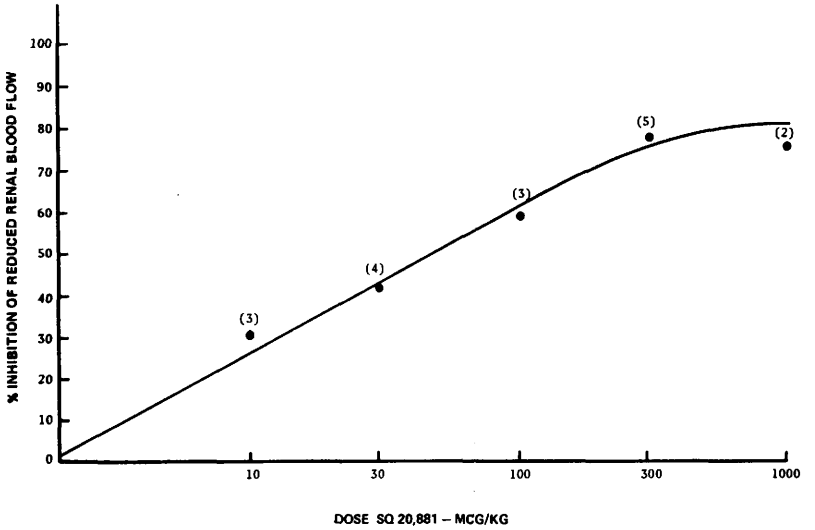

FIG. 2. Maximal inhibition of the angiotensin I-initiated reduction in renal blood flow by intravenous injections of SQ 20,881. Angiotensin I infused at 50 to 100 ng/kg/min. Points represent mean values of the number of doses in parentheses.

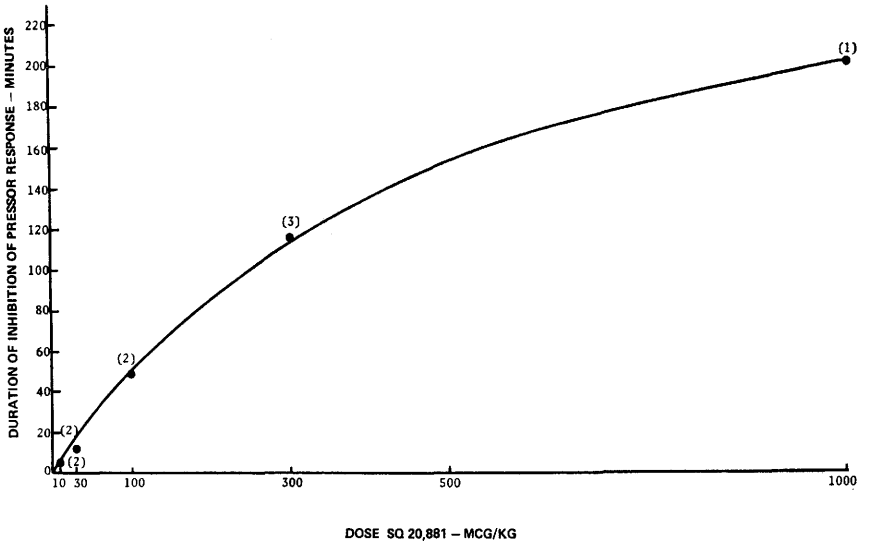

FIG. 3. Duration of ≧25% inhibition of the angiotensin I-initiated pressor response by intravenous injections of SQ 20,881. Angiotensin I infused at 50 to 100 ng/kg/min. Points represent mean values of the number of doses in parentheses.

the termination of the antagonistic effect of SQ 20,881. This finding suggests that there was no significant accumulation of angiotensin I during the period of inhibition of its enzymic alteration by SQ 20,881.

The data in this study on the inhibition by SQ 20,881 of the angiotensin I-initiated pressor response are in agreement with those of a previous investigation (5), although the experimental procedures were different. In the earlier study, SQ 20,881 inhibited transient increases in blood pressure produced by the rapid intravenous injection of angiotensin I. In the study reported here, a continuous

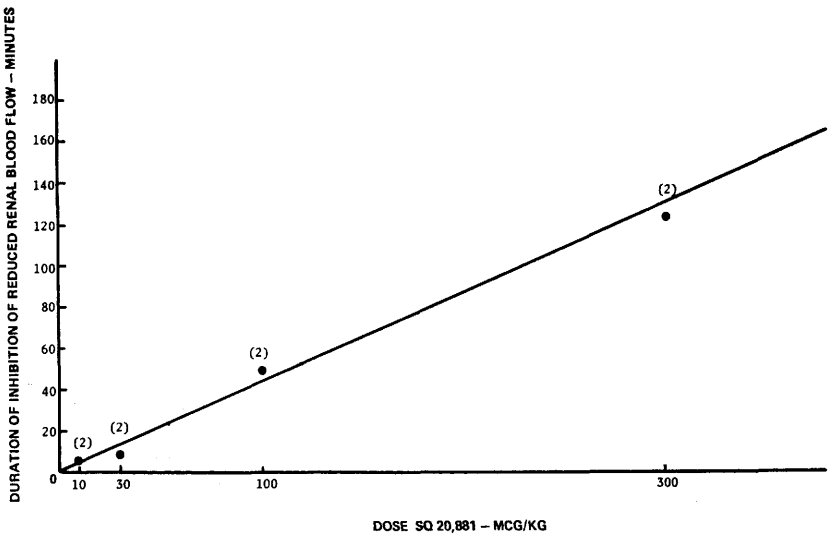

FIG. 4. Duration of ≧25% inhibition of the angiotensin I-initiated reduction in renal blood flow by intravenous injections of SQ 20,881. Angiotensin I infused at 50 to 100 ng/kg/min. Points represent mean values of the number of doses in parentheses.

pressor response maintained by a constant infusion of angiotensin I was inhibited by intravenous injections of SQ 20,881. In addition, this study demonstrated the inhibitory effect of SQ 20,881 on angiotensin I-initiated reduced renal blood flow.

Summary. Intravenous injections of SQ 20,881, a competitive inhibitor of the angiotensin-converting enzyme, suppressed the pressor and reduced renal blood flow responses initiated by the infusion of angiotensin I (50 to 100 ng/kg/min) into anesthetized dogs. Both the degree and duration of inhibition by SQ 20,881 were proportional to the dose of SQ 20,881 up to 300 μg/kg; this dose produced a maximal inhibition of about 80%, and an inhibition of at least 25% that lasted for approximately 2 hr.

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